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Please note: Dr. de Boer is a member of 2 steering committees of projects that are financed by GlaxoSmithKline and 2 umbrella organizations: the European Federation of Pharmaceutical Industries and Associations and the Association of the European Self-Medication Industry. These relationships are not relevant to the contents of this letter.

REFERENCE

1. Turakhia MP, Santangeli P, Winkelmayer WC, et al. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. J Am Coll Cardiol 2014;64:660–8.

REPLY: Increased Mortality by Digoxin in Patients With Atrial Fibrillation?

Dr. de Boer brings up some important design considerations regarding our analysis of the TREAT-AF (Retrospective Evaluation and Assessment of Therapies in AF) study (1). He correctly argues that there can be misclassification of digoxin exposure in our design. Our observational study was designed as an intention-to-treat analysis, comparing the strategies of use and nonuse of digoxin as initial or early therapy in patients with newly diagnosed atrial fibrillation (AF) (1). Although we found that 80% of patients in the digoxin arm were still on therapy at 1 year, there is a strong possibility of digoxin exposure in the control arm after 90 days. However, we believe this would not represent "misclassification" in an intention-to-treat design but rather crossover of therapy. Generally, crossover would bias toward the null and therefore would not likely account for the observed difference in outcomes.

Therapy crossover is common in management of AF and complicates analysis and interpretation of randomized trials. Crossover may be motivated by observed and unobserved confounders, which can further complicate analysis and may in part explain the seemingly incongruent results of 2 secondary analyses of digoxin using the same AFFIRM (AF Follow-Up Investigation of Rhythm Management) trial data set (2,3). Separating patients into exposed and unexposed blocks of person-time without adjusting for time-varying confounders could exaggerate treatment effect (or harm) (4). On the other hand, contemporary approaches such as marginal structural models that incorporate time-varying data can bias toward the null from overadjustment or model misspecification (5).

For these reasons, we elected to study a new disease cohort using an intention-to-treat design that evaluated digoxin as an initial treatment strategy. Our decision to adjust for adherence rather than to stratify was to account for variation in adherence in the overall point estimate. We agree that further work to explore the heterogeneity of treatment effects across strata of adherence and time course of therapy would be valuable and complementary.

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2. Whitbeck MG, Charnigo RJ, Khairy P, et al. Increased mortality among patients taking digoxin—analysis from the AFFIRM study. Eur Heart J 2013;34:1481–8.

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4. Murphy SA. When 'digoxin use' is not the same as "digoxin use": lessons from the AFFIRM trial. Eur Heart J 2013;34:1465–7.

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Patent Foramen Ovale and Paradoxical Systemic Embolism

Can We Determine High-Risk Characteristics by Echocardiography?

We read with interest the review paper on paradoxical embolism by Windecker et al. (1). It was suggested, on the basis of available evidence from published reports, that device closure of patent foramen ovale (PFO) should be considered in patients with first-time cryptogenic stroke, particularly in those with high-risk criteria, such as presence of an atrial septal aneurysm (ASA), large PFO, Eustachian valve, or Chiari network. The viewpoints of